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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.00      72.43

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=> s adenoviral vector

L20       5905 ADENOVIRAL VECTOR

=> s deletion (s) E1b

L21        384 DELETION (S) E1B

=> s p19

L22       6178 P19

=> s 55K

L23        966 55K

=> s pIX

L24        620 PIX

=> s TNF? (s) CD (s)

MISSING TERM AFTER CD (S
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Operators must be followed by a search term, L-number, or query name.

=> s TNF? (s) CD

L25 882 TNF? (S) CD

=> s L20 and L21 and L22 and L23 and L25

L26 0 L20 AND L21 AND L22 AND L23 AND L25

=> s L20 and L21 and L22

L27 0 L20 AND L21 AND L22

=> s L20 and L21

L28 21 L20 AND L21

=> duplicate remove L28

DUPLICATE PREFERENCE IS 'EMBASE, SCISEARCH, CAPLUS, MEDLINE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L28
L29 9 DUPLICATE REMOVE L28 (12 DUPLICATES REMOVED)

=> display total ibib abs L29

L29 ANSWER 1 OF 9 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2000068982 EMBASE
TITLE: **Deletion** of the adenoviral **E1b**-19kD gene enhances tumor cell killing of a replicating **adenoviral vector**.
AUTHOR: Sauthoff H.; Heitner S.; Rom W.N.; Hay J.G.
CORPORATE SOURCE: Dr. J.G. Hay, NYU School of Medicine, 550 First Avenue, New York, NY 10016, United States. john.hay@med.nyu.edu
SOURCE: Human Gene Therapy, (10 Feb 2000) 11/3 (379-388).
Refs: 47
ISSN: 1043-0342 CODEN: HGTHE3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
016 Cancer
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Replicating **adenoviral vectors** are a promising new modality for cancer treatment and clinical trials with such vectors are ongoing. Targeting these vectors to cancer cells has been the focus of research. However, even if perfect targeting were to be achieved, a vector still must effectively kill cancer cells and spread throughout the bulk of the tumor. The adenoviral **E1b**- 19kD protein is a potent inhibitor of apoptosis and may therefore compromise the therapeutic efficacy of an **adenoviral vector**. In this study we have investigated if an **E1b**-19kD gene **deletion** could improve the ability of a replicating **adenoviral vector** to spread through and kill cancer cells. In several lung cancer cell lines an **E1b**-19kD-deleted virus (Ad337) induced substantially more apoptosis than did a wild-type virus (Ad309), and tumor cell survival was

significantly reduced in three of four cell lines. In addition, the apoptotic effects of cisplatin or paclitaxel were augmented by Ad337, but inhibited by wild-type virus. The number of infectious virus particles in the supernatant of infected cells was increased with Ad337 compared with wild-type virus, indicating enhanced early viral release. Ad337, in contrast to Ad309, induced significantly larger plaques after infection of A549 cells. This well-described large plaque phenotype of an **E1b** -19kD mutant virus is likely the result of early viral release and enhanced cell-to-cell viral spread. Loss of **E1b**-19kD function caused only minor cell line-specific increase or decrease in viral yield. We conclude that **deletion** of the **E1b**-19kD gene may enhance the tumoricidal effects of a replicating **adenoviral vector**.

L29 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:723195 CAPLUS
DOCUMENT NUMBER: 131:318578
TITLE: Partially deleted **adenoviral vectors** with therapeutic expression potential for transgenes where delected vector genes are introduced within producer cell chromosome
INVENTOR(S): Wadsworth, Samuel C.; Scaria, Abraham
PATENT ASSIGNEE(S): Genzyme Corp., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957296	A1	19991111	WO 1999-US9590	19990430

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.:		
	US 1998-83841	19980501
	US 1999-118118	19990201

AB The invention is directed to novel partially deleted **adenoviral vectors** (DeAd) in which the majority of adenoviral early genes required for replication are deleted from the vector and placed within the chromosome of a producer cell line under conditional promoter control. Rephrased, the expression of genes encoding virion structural proteins is made conditional by replacement of the major late promoter with alternative promoters that can be controlled.. Moreover, the procedures described here is directed to DeAd vectors in which expression of genes encoding virion structural proteins in diminished by deletion the VA RNA genes from the vector. This system is applicable to human adenovirus 2, 5, 6, and 17. The partially deleted adenoviral (DeAd) vectors of the invention can accommodate inserts, such as transgenes, of up to 12-15 kb in size. The invention is further directed to DeAd vector producer cell lines that contain the adenoviral early genes necessary for replication under conditional promoter control that allow for large scale prodn. of vectors. This conditional promoter system includes control sequences from the dimerizer gene or tetracycline or ecdysone control systems. The invention is also directed to methods for the prodn. of DeAd vectors in such cell lines and to the use of such vectors to deliver transgenes to target cells. These transgenes include the CFTR and human .alpha.-galactosidase A and erythropoietin and factor VII and factor IX.

L29 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:359656 CAPLUS

DOCUMENT NUMBER: 131:14848
TITLE: Adenovirus-helper virus vector system using Sp1 and MAZ transcription factor regulation
INVENTOR(S): Parks, Christopher L.; Shenk, Thomas
PATENT ASSIGNEE(S): Princeton University, USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9927101	A1	19990603	WO 1998-US25361	19981125
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9915394	A1	19990615	AU 1999-15394	19981125
PRIORITY APPLN. INFO.:			US 1997-66295	19971125
			WO 1998-US25361	19981125

AB Claimed are **adenoviral vectors** prepd. by inserting exogenous nucleic acid between the terminal segments of the linear adenovirus genome, which include the viral origin of replication and packaging sequence genes. The vectors are based on adenovirus type 5, and are prepd. with a a helper adenovirus comprising a **deletion** of genes E1A and/or **E1B**. The helper virus contains a promoter with binding sites for the MAZ and Sp1 transcription factors. Co-transfection with the **adenoviral vector**, the helper vector, and administration of the MAZ and SP1 transcription factors produces expression of the exogenous nucleic acid.

L29 ANSWER 4 OF 9 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 1999311904 EMBASE
TITLE: p53 Selective and nonselective replication of an E1B-deleted adenovirus in hepatocellular carcinoma.
AUTHOR: Vollmer C.M.; Ribas A.; Butterfield L.H.; Dissette V.B.; Andrews K.J.; Eilber F.C.; Montejo L.D.; Chen A.Y.; Hu B.; Glaspy J.A.; McBride W.H.; Economou J.S.
CORPORATE SOURCE: J.S. Economou, Division of Surgical Oncology, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095-1782, United States.
jeconomo@surgery.medsch.ucla.edu
SOURCE: Cancer Research, (1 Sep 1999) 59/17 (4369-4374).
Refs: 21
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB An **E1B** gene-attenuated adenovirus (dl1520) has been proposed to have a selective cytolytic activity in cancer cells with a mutation or **deletion** in the p53 tumor suppressor gene (p53-null), a defect present in almost half of human hepatocellular carcinomas (HCCs). In this study, the in vitro and in vivo antitumor activity of dl1520 was investigated focusing on two human HCC cell lines, a p53-wild type (p53-wt) cell line and a p53-null cell line. dl1520 was tested for in vitro cytopathic effects and viral replication in the human HCC cell lines

Hep3B (p53-null) and HepG2 (p53-wt). The in vivo antitumor effects of dl1520 were investigated in tumors grown s.c. in a severe combined immunodeficient mouse model. In addition, the combination of dl1520 infection with systemic chemotherapy was assessed in these tumor xenografts. At low multiplicities of infection, dl1520 had an apparent p53- dependent in vitro viral growth in HCC cell lines. At higher multiplicities of infection, dl1520 viral replication was independent of the p53 status of the target cells. In vivo, dl1520 significantly retarded
the growth of the p53-null Hep3B xenografts, an effect augmented by the addition of cisplatin. However, complete tumor regressions were rare, and most tumors eventually grew progressively. dl1520 had no effect on the in vivo growth of the p53-wt HepG2 cells, with or without cisplatin treatment. The **E1B**-deleted **adenoviral vector**
dl1520 has an apparent p53-dependent effect in HCC cell lines. However, this effect is lost at higher viral doses and only induces partial tumor regressions without tumor cures in a human HCC xenograft model.

L29 ANSWER 5 OF 9 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 1999222721 EMBASE
TITLE: 'Autoreplication' of the vector genome in recombinant **adenoviral vectors** with different E1 region deletions and transgenes.
AUTHOR: Marienfeld U.; Haack A.; Thalheimer P.; Schneider-Rasp S.; Brackmann H.-H.; Poller W.
CORPORATE SOURCE: W. Poller, Department Cardiology and Pneumology, Univ. Hospital Benjamin Franklin, Freie Universitat Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany
SOURCE: Gene Therapy, (1999) 6/6 (1101-1113).
Refs: 38
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB High transgene stabilities of 1 year and more have been reported in immunodeficient hosts after adenovirus mediated gene transfer. Transgene persistence of this duration could be due to inherently high stability of the episomal viral vector DNA. An alternative explanation would be limited
'autoreplication' of transgenic vector DNA, just sufficient counteract slow but continuous degradation within the host cells. Autoreplication could occur in the absence of any production of infectious virus particles, based on residual activity of the adenoviral DNA replication system only. To test this hypothesis, a series of DNA metabolic labeling studies in non-permissive cells cultures transfected with different vectors was conducted. Due to extensive E1 region **deletions** none of the vectors was able to produce viral progeny in non-permissive cells. Vectors fell into two categories, however, with respect to their autoreplication potential. Neosynthesis of vector DNA in non-permissive vector-transfected cells was readily detectable in 'type A' but not in 'type B' vectors. In addition to their different transgene expression cassettes, vector DNA sequencing showed a less extensive E1 **deletion** in type A (nucleotides 453-3333 of wild-type virus) as compared to type B vectors (nucleotides 325-3523). Autoreplication was also associated with high transcriptional activity of several viral genes (**E1B**-14k, adenoviral DNA polymerase, single-strand DNA-binding protein, E4-25k), in contrast to type B vectors. In addition to these 'wild-type' transcripts, 'irregular' recombinant transcripts were detected
in autoreplication vectors which contained the transgenic cDNA in conjunction with **adenoviral vector** sequences.
Exogenous or cryptic promoters may (under certain conditions) enhance the

transcriptional activity of a vector in such a way that autoreplication occurs. Conditions determining the level of transcriptional enhancement (extent of E1 **deletion**, type of promoter and transgene, etc) need to be further defined before rational design of adenovectors with high autoreplication capacity becomes possible. In summary, we have shown autoreplication to be a novel feature of certain E1-deleted adenovectors with likely relevance for their stability in vivo, but also with possibly adverse consequences for target cell function or vector immunogenicity. Full characterization of **adenoviral vector** systems should therefore include a description of their autoreplication capacity.

L29 ANSWER 6 OF 9 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 2000:4504 SCISEARCH
THE GENUINE ARTICLE: 265JR
TITLE: **Deletion** of the **E1b**-19-kDa gene enhances the tumoricidal effect of a replicating **adenoviral vector**
AUTHOR: Sauthoff K (Reprint); Heitner S; Rom W N; Hay J G
CORPORATE SOURCE: NYU, SCH MED, DEPT MED, DIV PULM & CRIT CARE MED, NEW YORK, NY; NYU, SCH MED, DEPT PATHOL, DIV PULM & CRIT CARE MED, NEW YORK, NY
COUNTRY OF AUTHOR: USA
SOURCE: CANCER GENE THERAPY, (NOV-DEC 1999) Vol. 6, No. 6, Supp. [S], pp. O38-O38.
Publisher: STOCKTON PRESS, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707.
ISSN: 0929-1903.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L29 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:550499 CAPLUS
DOCUMENT NUMBER: 129:157708
TITLE: An oncolytic/immunogenic complementary-**adenoviral vector** system
INVENTOR(S): Alemany, Ramon; Fang, Xiangming; Zhang, Wei-Wei
PATENT ASSIGNEE(S): Baxter International Inc., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9835028	A2	19980813	WO 1998-US1301	19980123
WO 9835028	A3	19981022		
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 968281	A2	20000105	EP 1998-904658	19980123
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-797160 19970210
WO 1998-US1301 19980123

AB This invention encompasses a compn. for killing target cells, such as tumor cells. The compn. comprises a first and a second **adenoviral vector** that have complementary function and are mutually dependent on each other for replication in a target cell. One of said **adenoviral vectors** has a target cell-activated promoter or a functional deletion that controls and limits propagation of the **adenoviral vectors** in the target cells which directly or

indirectly kills the target cells. One of the **adenoviral vectors** comprises a gene encoding a protein which is expressed in the target cells and can induce anticancer immune responses. The target cells may be hepatoma, breast cancer, melanoma, colon cancer, or prostate cancer cells, for example. The vectors of this invention may also be utilized to treat other diseases such as restenosis, in which case the target cell may be a vascular smooth muscle cell, for example.

L29 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:111187 CAPLUS
DOCUMENT NUMBER: 126:113179
TITLE: Gene therapy for myocardial ischemia
INVENTOR(S): Giordano, Frank J.; Dillmann, Wolfgang H.; Mestril, Ruben
PATENT ASSIGNEE(S): Regents of the University of California, USA; Giordano, Frank J.; Dillmann, Wolfgang H.; Mestril, Ruben
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640195	A1	19961219	WO 1996-US9858	19960607
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
CA 2174040	AA	19971013	CA 1996-2174040	19960412
CA 2221710	AA	19961219	CA 1996-2221710	19960607
AU 9662681	A1	19961230	AU 1996-62681	19960607
EP 831874	A1	19980401	EP 1996-921461	19960607
R: DE, ES, FR, GB, IT				
PRIORITY APPLN. INFO.:			US 1995-481122	19950607
			WO 1996-US9858	19960607

AB A transgene-inserted replication-deficit **adenoviral vector** is effectively used in in vivo gene therapy for myocardial ischemia in an protective way, by a single intracoronary injection directly conducted deeply in the lumen of the coronary arteries in an amt.
sufficient for transfecting all cell types in the affected region, including cardiac myocytes. The vector contains a transgene coding for a stress-related factor (HSP70i, HSP27, etc.).

L29 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:738180 CAPLUS
DOCUMENT NUMBER: 126:2494
TITLE: An adenovirus vector capable of expressing up to 36 kB
heterologous DNA, a helper virus, and gene therapy
INVENTOR(S): Zhang, Wei-Wei; Alemany, Ramon
PATENT ASSIGNEE(S): University of Texas System, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9633280		A1	19961024	WO 1996-US5310	19960417
W:	AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
CA 2218610		AA	19961024	CA 1996-2218610	19960417
AU 9655519		A1	19961107	AU 1996-55519	19960417
EP 821739		A1	19980204	EP 1996-912839	19960417
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11503910		T2	19990406	JP 1996-531882	19960417
PRIORITY APPLN. INFO.:				US 1995-423573	19950417
				WO 1996-US5310	19960417

AB An adenoviral helper viruses system is disclosed that is capable of expressing up to 36 kB of heterologous DNA in a replication defective **adenoviral vector**. The system comprises **adenoviral vector** constructs, one or more helper viruses and a helper cell line. The vector construct is capable of being replicated and packaged into a virion particle in the helper cell when coinfected with a helper virus that contains a defective packaging signal.

In particular, the helper cell expresses DNA from one or more of the "early" codings regions of the adenovirus 5 genome (Ad5) and one or more helper viruses express DNA from one or more of the "early" coding regions and all of the later coding regions of the Ad5 genome, complementing mutations in the corresponding regions of the vector. Also disclosed are methods of transferring heterologous DNA-contg. vectors into mammalian cells.

=> file stnguide

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CA SUBSCRIBER PRICE	-2.78	-2.78

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=> s adenoviral vector

L20       5905 ADENOVIRAL VECTOR

=> s deletion (s) E1b

L21        384 DELETION (S) E1B

=> s p19

L22       6178 P19

=> s 55K

L23        966 55K

=> s pIX

L24        620 PIX

=> s TNF? (s) CD (s)

MISSING TERM AFTER CD (S
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                   EPO, and German patents
 NEWS  3   Feb  1  Addition of Machine-Translated Abstracts to CAplus
 NEWS  4   Feb  2  STEREO BOND SEARCH PROBLEM FIXED WITH STN EXPRESS 5.0C
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 NEWS  6   Feb 16  BIOTECHNOBASE NOW ON STN
 NEWS  7   Feb 22  New Database Producer Clusters Now Available on STN
 NEWS  8   Feb 28  Structure Search Limits Increased in REGISTRY,
                   ZREGISTRY, and CASREACT
 NEWS  9   Feb 28  Patent Information Now Searchable in CAOLD
 NEWS 10   Mar  1  New IMSDIRECTORY Provides Pharma Company Details
 NEWS 11   Mar 20  INPADOC: PRODUCER WARNING ABOUT DATA DELAYS
 NEWS 12   Mar 22  NEW FEATURES IN INPADOC - RANGE SEARCHING AND NEW
                   SDI/UPDATE SEARCH FIELD

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=> s Poller/AU ran = 1985

L2             0 POLLER/AU

=> s Poller W? and Germany/SO ran = 1990

               0 "POLLER"
          222045 W?
               0 POLLER W?
                   ("POLLER"(W)W?)
              19 GERMANY/SO
L3             0 POLLER W? AND GERMANY/SO

=> file embase

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FULL ESTIMATED COST                                    10.80      10.95

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 substance identification.

=> e poller W/AU

E1             1     POLLER S/AU
E2             8     POLLER U/AU
E3            37 --> POLLER W/AU
E4             2     POLLER W C/AU
E5             2     POLLER W R/AU
E6             2     POLLERA C/AU
E7            24     POLLERA C F/AU
E8            20     POLLERA M/AU
E9             1     POLLERA ORSUCCI M/AU
E10            1     POLLERBERG A/AU
E11            1     POLLERBERG E/AU
E12            2     POLLERBERG E G/AU

=> s E3-E5

              37 "POLLER W"/AU
               2 "POLLER W C"/AU
               2 "POLLER W R"/AU
L4            41 ("POLLER W"/AU OR "POLLER W C"/AU OR "POLLER W R"/AU)

=> s L4 and PY>1990

         3516989 PY>1990
L5            32 L4 AND PY>1990

=> s L5 and adenoviral
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1987 ADENOVIRAL
L6 7 L5 AND ADENOVIRAL

=> display total ibib abs L6

L6 ANSWER 1 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999368188 EMBASE
TITLE: Highly sensitive and species-specific assay for quantification of human transgene expression levels.
AUTHOR: Haack A.; **Poller W.**; Schneider-Rasp S.; Thalheimer P.; Schmitt C.; Hanfland P.; Brackmann H.-H.; Schwaab R.
CORPORATE SOURCE: Dr. A. Haack, Inst. Exptl. Haematol. Transfu. Med., University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany
SOURCE: Haemophilia, (1999) 5/5 (334-339).
Refs: 15
ISSN: 1351-8216 CODEN: HAEMF4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB During the past few years great efforts have been made to construct and to test human factor VIII (hFVIII) and IX (hFIX) vectors suitable for haemophilia gene therapy in vivo. However, little is known about the molecular mechanisms of persistence and shut-off of transgene expression in the target organs after gene transfer using recombinant **adenoviral** vectors. To evaluate low transgene mRNA levels in different tissues, especially at long times after the gene transfer, the common northern blot method is often not sensitive enough. For this reason we developed a new, highly sensitive and species-specific method for hFIX mRNA quantification and employed it in mice treated with an **adenoviral** vector (Ad5CMVFIX) expressing human FIX. In addition to its very high sensitivity (lowest detection level = 1 fg RNA), the method was shown to be strictly species-specific, since hFIX mRNA signals were never detected in untreated mice. In a long-term study of 18 vector-treated mice we compared the human FIX:Ag levels in the mouse plasma, the human FIX mRNA levels and human FIX vector DNA concentrations in the mouse liver. We found that a slow but continuous decrease of hFIX:Ag levels in mouse plasma was associated with corresponding decrease of hFIX mRNA levels in the liver. However, the Ad5CMVFIX vector DNA levels did not decrease to a comparable degree, suggesting that the decrease of human FIX:Ag levels in mouse plasma is, to a significant extent, also caused by CMV promotor shut-off and only to a minor degree by loss of vector DNA.

L6 ANSWER 2 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999344920 EMBASE
TITLE: Expression of Coxsackie adenovirus receptor and alpha(v)-integrin does not correlate with aconovector targeting in vivo indicating anatomical vector barriers.
AUTHOR: Fechner H.; Haack A.; Wang H.; Wang X.; Eizema K.; Pauschinger M.; Schoemaker R.G.; Van Veghel R.; Houtsmuller A.B.; Schultheiss H.-P.; Lamers J.M.J.; **Poller W.**
CORPORATE SOURCE: H. Fechner, Department Cardiology and Pneumology, University Hosp. Benjamin Franklin, Freie Universitat Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany

SOURCE: Gene Therapy, (1999) 6/9 (1520-1535).
Refs: 69
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Recombinant **adenoviral** vectors are broadly applied in gene therapy protocols. However, adenovector-mediated gene transfer has limitations in vivo. One of these is the low gene transfer rate into organs other than the liver after systemic intravenous vector injection. Local direct injection into the target organ has been used as one possible solution, but increases necessary equipment and methodology and is traumatic to the target. Wild-type adenovirus infection as well as adenovector-mediated gene transfer depends on virus interaction with the Coxsackie adenovirus receptor (CAR) mediating virus attachment to the cell surface, and on interaction with .alpha.(v).beta.3 and .alpha.(v).beta.5 integrins mediating virus entry into the cell. In order to assess the receptor-associated potential of different tissues to act as adenovector targets, we have therefore determined CAR and .alpha.(v)-integrin expression in multiple organs from different species. In addition, we have newly determined several human, rat, pig and dog CAR-mRNA sequences. Sequence comparison and structural analyses of known and of newly determined sequences suggests a potential adenovirus binding site between amino acids 29 and 128 of the CAR. With respect to the virus receptor expression patterns we found that CAR-mRNA expression was extremely variable between different tissues, with the highest levels in the liver, whereas .alpha.(v)-integrin expression was far more homogenous among different organs. Both CAR and .alpha.(v)-integrin showed similar expression patterns among different species. There was no correlation, however, between the adenovector expression patterns after intravenous, intracardiac and aortic root injection, respectively, and the virus receptor patterns. In summary, many organs carry both receptors required to make them potential adenovector targets. In sharp contrast, their actual targeting clearly indicates that adenovirus receptor expression is necessary but not sufficient for vector transfer after systemic injection.
The apparently very important role of anatomical barriers, in particular the endothelium, requires close attention when developing non-traumatic, organ-specific gene therapy protocols.

L6 ANSWER 3 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999283875 EMBASE
TITLE: Biochemical and functional characterization of nitric oxide synthase III gene transfer using a replication-deficient **adenoviral** vector.
AUTHOR: Frey A.; Schneider-Rasp S.; Marienfeld U.; Yu J.C.-M.; Paul M.; **Poller W.**; Schmidt H.H.H.
CORPORATE SOURCE: Prof. H.H.H. Schmidt, Dept. Pharmacology and Toxicology, Julius-Maximilians-University, Versbacher Strasse 9, D-97078 Wurzburg, Germany. schmidt@toxi.uni-wuerzburg.de
SOURCE: Biochemical Pharmacology, (1999) 58/7 (1155-1166).
Refs: 44
ISSN: 0006-2952 CODEN: BCPCA6
PUBLISHER IDENT.: S 0006-2952(99)00196-3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics

029 Clinical Biochemistry
030 Pharmacology
004 Microbiology

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Nitric oxide (NO) produced in endothelial cells has been implicated in the regulation of blood pressure, regional blood flow, inhibition of platelet aggregation, and endothelial and vascular smooth muscle cell proliferation. In a variety of cardiovascular disease states, such as atherosclerosis, arterial hypertension, and restenosis, expression of endothelial NO synthase (NOS-III) and endothelial NO production appear to be altered. Thus, NOS-III is an attractive target for cardiovascular gene therapy for which **adenoviral** vectors are one of the most effective vector systems. Therefore, a recombinant **adenoviral** vector expressing NOS-III (adenovirus type 5 [Ad5] cytomegalovirus [CMV] NOSIII) was constructed and biochemically and pharmacologically characterized both in vitro and in intact cells. Ad5CMVNOSIII-derived recombinant NOS-III was successfully expressed, as shown by immunoprecipitation and immunocytochemistry, and biologically active, as shown by functional assays in human primary umbilical vein and EA.hy926 endothelial cells, as well as 293 human embryonic kidney and Chinese hamster ovary cells. The K(m) values for NADPH and L-arginine and the K(a) for tetrahydrobiopterin as well as the enzyme's dependency on other cofactors were similar to recombinant reference enzyme and literature values. NOS-III expression levels correlated linearly with the multiplicity of infection with Ad5CMVNOSIII and lasted for at least 8 days. NOS-III transfection inhibited endothelial cell proliferation. In conclusion, adenovirus-mediated gene transfer of Ad5CMVNOSIII to vascular and non-vascular cells resulted in the dose-dependent expression of intact, physiologically regulated, and functionally active NOS-III.

L6 ANSWER 4 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999222721 EMBASE
TITLE: 'Autoreplication' of the vector genome in recombinant **adenoviral** vectors with different E1 region deletions and transgenes.
AUTHOR: Marienfeld U.; Haack A.; Thalheimer P.; Schneider-Rasp S.; Brackmann H.-H.; **Poller W.**
CORPORATE SOURCE: W. Poller, Department Cardiology and Pneumology, Univ. Hospital Benjamin Franklin, Freie Universitat Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany
SOURCE: Gene Therapy, (1999) 6/6 (1101-1113).
Refs: 38
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB High transgene stabilities of 1 year and more have been reported in immunodeficient hosts after adenovirus mediated gene transfer. Transgene persistence of this duration could be due to inherently high stability of the episomal viral vector DNA. An alternative explanation would be limited 'autoreplication' of transgenic vector DNA, just sufficient counteract slow but continuous degradation within the host cells. Autoreplication could occur in the absence of any production of infectious virus particles, based on residual activity of the **adenoviral** DNA replication system only. To test this hypothesis, a series of DNA metabolic labeling studies in non-permissive cells cultures transfected with different vectors was conducted. Due to extensive E1 region deletions

none of the vectors was able to produce viral progeny in non-permissive cells. Vectors fell into two categories, however, with respect to their autoreplication potential. Neosynthesis of vector DNA in non-permissive vector-transfected cells was readily detectable in 'type A' but not in 'type B' vectors. In addition to their different transgene expression cassettes, vector DNA sequencing showed a less extensive E1 deletion in type A (nucleotides 453-3333 of wild-type virus) as compared to type B vectors (nucleotides 325-3523). Autoreplication was also associated with high transcriptional activity of several viral genes (E1B-14k, **adenoviral** DNA polymerase, single-strand DNA-binding protein, E4-25k), in contrast to type B vectors. In addition to these 'wild-type' transcripts, 'irregular' recombinant transcripts were detected in autoreplication vectors which contained the transgenic cDNA in conjunction with **adenoviral** vector sequences. Exogenous or cryptic promoters may (under certain conditions) enhance the transcriptional activity of a vector in such a way that autoreplication occurs. Conditions determining the level of transcriptional enhancement (extent of E1 deletion, type of promoter and transgene, etc) need to be further defined before rational design of adenovectors with high autoreplication capacity becomes possible. In summary, we have shown autoreplication to be a novel feature of certain E1-deleted adenovectors with likely relevance for their stability in vivo, but also with possibly adverse consequences for target cell function or vector immunogenicity. Full characterization of **adenoviral** vector systems should therefore include a description of their autoreplication capacity.

L6 ANSWER 5 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998254159 EMBASE
TITLE: Endogenous or overexpressed cGMP-dependent protein kinases inhibit cAMP- dependent renin release from rat isolated perfused kidney, microdissected glomeruli, and isolated juxtaglomerular cells.
AUTHOR: Gambaryan S.; Wagner C.; Smolenski A.; Walter U.; **Poller W.**; Haase W.; Kurtz A.; Lohmann S.M.
CORPORATE SOURCE: S. Gambaryan, Medizinische Universitats-Klinik, Klin. Biochem./Pathobiochem. Inst., 97080 Wurzburg, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (21 Jul 1998) 95/15 (9003-9008). Refs: 34
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 002 Physiology
028 Urology and Nephrology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB An overactive renin-angiotensin-aldosterone system (RAAS) has a central role in the pathogenesis of hypertension and cardiac hypertrophy, precursors of cardiac failure. Natriuretic peptides and NO acting through their second messenger, cGMP, increase natriuresis and diuresis, and inhibit renin release; however the mechanism by which this inhibition of the RAAS system functions is obscure. We recently reported cloning of the cDNA for type II cGMP-dependent protein kinase (cGK II), elucidated its first known function of inhibiting the cystic fibrosis transmembrane conductance regulator in rat intestine, and initially described its location in rat kidney juxtaglomerular (JG) cells, the ascending thin limb, and the brush border of proximal tubules. Here, we demonstrate inhibition of isoproterenol- or forskolin- stimulated renin release by 8-para-chlorophenylthio-cGMP (8-pCPT-cGMP), a selective activator of cGK, and prevention of this inhibition by a selective inhibitor of cGK, Rp-8-pCPT-cGMPS. In systems of differing complexity, inhibition by 8-pCPT-cGMP was nearly complete in isolated perfused kidney and microdissected afferent arterioles but only .simeq.25% in isolated JG

cells. Expression of either cGK II or cGK I in JG cells by using **adenoviral** vectors enhanced the inhibition of forskolin-stimulated renin release by 8-pCPT-cGMP to 50%. Our results indicate that cGK II, and possibly cGK I, can mediate cGMP inhibitory effects on renin release and are physiological components of the cGMP signal transduction system which opposes the RAAS.

L6 ANSWER 6 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97054706 EMBASE
DOCUMENT NUMBER: 1997054706
TITLE: cGMP stimulation of cystic fibrosis transmembrane conductance regulator Cl- channels co-expressed with cGMP-dependent protein kinase type II but not type I.beta..
AUTHOR: Vaandrager A.B.; Tilly B.C.; Smolenski A.; Schneider-Raspi S.; Bot A.G.M.; Edixhoven M.; Scholte B.J.; Jarchau T.; Walter U.; Lohmann S.M.; **Poller W.C.**; De Jonge H.R.
CORPORATE SOURCE: A.B. Vaandrager, Dept. of Biochemistry, Medical Faculty, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands
SOURCE: Journal of Biological Chemistry, (1997) 272/7 (4195-4200). Refs: 33
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In order to investigate the involvement of cGMP-dependent protein kinase (cGK) type II in cGMP-provoked intestinal Cl- secretion, cGMP-dependent activation and phosphorylation of cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channels was analyzed after expression of cGK II or cGKIss in intact cells. An intestinal cell line which stably expresses CFTR (IEC-CF7) but contains no detectable endogenous cGK II was infected with a recombinant **adenoviral** vector containing the cGK II coding region (Ad-cGK II) resulting in co-expression of active cGK II. In these cells, CFTR was activated by membrane-permeant analogs of cGMP or by the cGMP-elevating hormone atrial natriuretic peptide as measured by 125I- efflux assays and whole-cell patch clamp analysis. In contrast, infection with recombinant adenoviruses expressing cGK I.beta. or luciferase did not convey cGMP sensitivity to CFTR in IEC-CF7 cells. Concordant with the activation of CFTR by only cGK II, infection with Ad-cGK II but not Ad-cGK I.beta. enabled cGMP analogs to increase CFTR phosphorylation in intact cells. These and other data provide evidence that endogenous cGK II is a key mediator of cGMP-provoked activation of CFTR in cells where both proteins are colocalized, e.g. intestinal epithelial cells. Furthermore, they demonstrate that neither the soluble cGK I.beta. nor cAMP-dependent protein kinase are able to substitute for cGK II in this cGMP-regulated function.

L6 ANSWER 7 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96202087 EMBASE
DOCUMENT NUMBER: 1996202087
TITLE: Stabilization of transgene expression by incorporation of E3 region genes into an **adenoviral** factor IX vector and by transient anti-CD4 treatment of the host.
AUTHOR: **Poller W.**; Schneider-Rasp S.; Liebert U.; Merklein F.; Thalheimer P.; Haack A.; Schwaab R.; Schmitt C.; Brackmann H.-H.
CORPORATE SOURCE: Medical University Clinic, University of Wurzburg, Josef-Schneiner-Strasse 2,D-97080 Wurzburg, Germany

SOURCE: Gene Therapy, (1996) 3/6 (521-530).
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Complex interactions between replication deficient **adenoviral** vectors (Ad5) and the immune system of the host influence the stability of transgenes in vivo. Vector-infected cells are attacked by diverse cellular immune mechanisms which limit transgene persistence. On the other hand, the products of several E3 region genes of wild-type adeno-virus can suppress host immune reactions by interference with the expression of MHC class I molecules and by other mechanisms. We have developed an **adenoviral** vector for human factor IX (Ad5.DELTA.E3+FIX) which carries the E3 region of wild-type adenovirus, and an E3-deleted vector of otherwise similar structure (Ad5.DELTA.E3FIX). Intravenous injection of Ad5E3+FIX in C57BI/6 mice resulted in expression levels up to 6000 ng/ml of recombinant human factor IX in the mouse plasma and in enhanced transgene stability as compared with the vector Ad5.DELTA.E3FIX. Whereas expression from E3-deleted vectors was essentially turned off 8 weeks after the gene transfer, the vector Ad5E3+FIX supported transgene expression with therapeutic levels of human factor IX in the mouse plasma for > 4 months. The enhanced stability of the vector Ad5E3+FIX appears to be a consequence of efficient E3 region-mediated suppression of the host's antivector immune response. As an additional approach to improving transgene stability the influence of transient CD4+ T cell depletion of the host was investigated. CD4+ cytotoxic T lymphocytes, contribute to the clearance of adenovirus-infected cells and play a pivotal role in the activation of CD8+ cytotoxic T cells and as helper T cells in the formation of human adenovirus neutralizing antibodies (HANA). Transient anti-CD4 treatment of the host limited to the time of vector injection resulted in a significant prolongation of transgene expression from the factor IX vector Ad5E3+FIX and a luciferase vector Ad5Luc. The combination of transient anti-CD4 treatment of the host and integration of a complete E3 region in an **adenoviral** vector resulted in markedly improved transgene stability after gene transfer to the liver (therapeutic factor IX levels for > 6 months).

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FILE LAST UPDATED: 27 Apr 2000  (20000427/ED)

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=> e poller w/AU

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E3           13 --> POLLER W/AU
E4            9     POLLER WOLFGANG/AU
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E6            2     POLLER WOLFGANG CHRISTIAN/AU
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E8            2     POLLERA C F/AU
E9            1     POLLERA CAMILLO/AU
E10           2     POLLERA CAMILLO F/AU
E11           1     POLLERA CLAUDIA/AU
E12          17     POLLERA M/AU

=> s E3-E6

             13 "POLLER W"/AU
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              1 "POLLER WOLFGANG C"/AU
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L7           25 ("POLLER W"/AU OR "POLLER WOLFGANG"/AU OR "POLLER WOLFGANG
C"/AU
                 OR "POLLER WOLFGANG CHRISTIAN"/AU)

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L8           0 L7 AND PY<1999 AND "POLLER U"/AU

=> s L7 and E1

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L9           0 L7 AND "POLLER U"/AU

=> s L7

             13 "POLLER W"/AU
              9 "POLLER WOLFGANG"/AU
              1 "POLLER WOLFGANG C"/AU
              2 "POLLER WOLFGANG CHRISTIAN"/AU
L10          25 ("POLLER W"/AU OR "POLLER WOLFGANG"/AU OR "POLLER WOLFGANG
C"/AU
                 OR "POLLER WOLFGANG CHRISTIAN"/AU)

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=> file embase, scisearch, caplus, biosis

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=> file medline, scisearch, caplus, biosis, embase

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=> s adenoviral (s) E1B or E1b or E1b genes or E1B genes (s) deletion

L11        3410 ADENOVIRAL (S) E1B OR E1B OR E1B GENES OR E1B GENES (S)
DELETION

=> s L11 and PY<1999

   2 FILES SEARCHED...
   4 FILES SEARCHED...
L12        2982 L11 AND PY<1999

=> s shuttle vectors and L12
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TI Six mutations in the glucokinase gene identified in MODY by using a nonradioactive sensitive screening technique

AU Hager, Joerg; Blanche, Helene; Sun, Fang; Vaxillaire, Nathalie Vionnet Martine; **Poller, Wolfgang**; Cohen, Daniel; Czernichow, Paul; Velho, Gilberto; Robert, Jean Jacques; et al.

CS Hum. Polymorphism Study Cent., Hop. Necker-Enfants Mal., Paris, 75010, Fr.

SO Diabetes (1994), 43(5), 730-3
CODEN: DIAEAZ; ISSN: 0012-1797

DT Journal

LA English

CC 14-8 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

AB The authors have reported that 56% of French families with maturity-onset diabetes of the young (MODY) carry a mutation in the glucokinase gene (GCK). Therefore, the authors have estd. a quick and sensitive nonradioactive technique (with the PhastSystemTM based on single-strand conformation polymorphism [SSCP] anal.) to routinely screen the 12 exons of GCK for mutations. The authors have studied GCK in 12 young hyperglycemic patients with a strong family history of type II diabetes. SSCP variants were obsd. in 6 of those 12 patients (50%), which cosegregated with diabetes in five families where DNA from addnl. members was available. Direct sequencing identified a 10-bp (base pair) deletion in exon 3; a 33-bp deletion at the exon 5/intron 5 junction, including the two consensus bases (GT) of the donor splice site; a nonsense mutation in exon 5 (Arg186 .fwdarw. Stop) in a Black-African family, which has been identified previously in a Caucasian family; and three missense mutations: Thr209 .fwdarw. Met209 in exon 6, Gly261 .fwdarw. Glu261 in exon 7, and Arg36 .fwdarw. Trp36 in exon 2. The missense mutation in exon 2 was found only in the second and third generation of the tested family but not in the first. To the authors' knowledge, this is the first time that a de novo mutation of GCK is reported within a family. All six families carrying a mutation in GCK were typical MODY and most of their affected members had a mild form of diabetes. This nonradioactive SSCP technique may be useful to routinely diagnose glucokinase deficiency, which is an important cause of hyperglycemia among young type II diabetic patients.

ST glucokinase gene mutation detection MODY disease

IT Gene, animal
RL: BIOL (Biological study)
(for glucokinase, detection of mutations in, in humans with maturity-onset diabetes of the young, SSCP using nonradioactive PhastSystem in)

IT Mutation
(in glucokinase gene, in humans with maturity-onset diabetes of the young, detection of, by SSCP using nonradioactive PhastSystem)

IT Genetic polymorphism
(single-strand conformation, glucokinase gene mutations in humans with maturity-onset diabetes of the young detected by, using nonradioactive PhastSystem)

IT Diabetes mellitus
(MODY (maturity-onset diabetes of the young), glucokinase gene mutations in, in humans, detection of, SSCP using nonradioactive PhastSystem in)

IT 9001-51-8, Glucokinase
RL: BIOL (Biological study)
(gene for, detection of mutations in, in humans with maturity-onset diabetes of the young, SSCP using nonradioactive PhastSystem in)

L10 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2000 ACS

TI A leucine-to-proline substitution causes a defective .alpha.1-antichymotrypsin allele associated with familial obstructive lung disease

AN 1994:188562 CAPLUS

contrast to Ad309, induced significantly larger plaques after infection of A549 cells. This well-described large plaque phenotype of an **E1b**-19kD mutant virus is likely the result of early viral release and enhanced cell-to-cell viral spread. Loss of **E1b**-19kD function caused only minor cell line-specific increase or decrease in viral yield. We conclude that **deletion** of the **E1b**-19kD gene may enhance the tumoricidal effects of a replicating **adenoviral vector**.

L29 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:723195 CAPLUS
DOCUMENT NUMBER: 131:318578
TITLE: Partially deleted **adenoviral vectors** with therapeutic expression potential for transgenes where delected vector genes are introduced within producer cell chromosome
INVENTOR(S): Wadsworth, Samuel C.; Scaria, Abraham
PATENT ASSIGNEE(S): Genzyme Corp., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957296	A1	19991111	WO 1999-US9590	19990430
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRIORITY APPLN. INFO.:			US 1998-83841	19980501
			US 1999-118118	19990201

AB The invention is directed to novel partially deleted **adenoviral vectors** (DeAd) in which the majority of adenoviral early genes required for replication are deleted from the vector and placed within the chromosome of a producer cell line under conditional promoter control. Rephrased, the expression of genes encoding virion structural proteins is made conditional by replacement of the major late promoter with alternative promoters that can be controlled.. Moreover, the procedures described here is directed to DeAd vectors in which expression of genes encoding virion structural proteins in diminished by deletion the VA RNA genes from the vector. This system is applicable to human adenovirus 2, 5, 6, and 17. The partially deleted adenoviral (DeAd) vectors of the invention can accommodate inserts, such as transgenes, of up to 12-15 kb in size. The invention is further directed to DeAd vector producer cell lines that contain the adenoviral early genes necessary for replication under conditional promoter control that allow for large scale prodn. of vectors. This conditional promoter system includes control sequences from the dimerizer gene or tetracycline or ecdysone control systems. The invention is also directed to methods for the prodn. of DeAd vectors in such cell lines and to the use of such vectors to deliver transgenes to target cells. These transgenes include the CFTR and human .alpha.-galactosidase A and erythropoietin and factor VII and factor IX.

L29 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:359656 CAPLUS
DOCUMENT NUMBER: 131:14848
TITLE: Adenovirus-helper virus vector system using Sp1 and MAZ transcription factor regulation
INVENTOR(S): Parks, Christopher L.; Shenk, Thomas
PATENT ASSIGNEE(S): Princeton University, USA

SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9927101	A1	19990603	WO 1998-US25361	19981125
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9915394	A1	19990615	AU 1999-15394	19981125
PRIORITY APPLN. INFO.:			US 1997-66295	19971125
			WO 1998-US25361	19981125

AB Claimed are **adenoviral vectors** prepd. by inserting exogenous nucleic acid between the terminal segments of the linear adenovirus genome, which include the viral origin of replication and packaging sequence genes. The vectors are based on adenovirus type 5, and are prepd. with a a helper adenovirus comprising a **deletion** of genes E1A and/or **E1B**. The helper virus contains a promoter with binding sites for the MAZ and Sp1 transcription factors. Co-transfection with the **adenoviral vector**, the helper vector, and administration of the MAZ and SP1 transcription factors produces expression of the exogenous nucleic acid.

L29 ANSWER 4 OF 9 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 1999311904 EMBASE
TITLE: p53 Selective and nonselective replication of an E1B-deleted adenovirus in hepatocellular carcinoma.
AUTHOR: Vollmer C.M.; Ribas A.; Butterfield L.H.; Dissette V.B.; Andrews K.J.; Eilber F.C.; Montejo L.D.; Chen A.Y.; Hu B.; Glaspy J.A.; McBride W.H.; Economou J.S.
CORPORATE SOURCE: J.S. Economou, Division of Surgical Oncology, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095-1782, United States.
jeconomo@surgery.medsch.ucla.edu
SOURCE: Cancer Research, (1 Sep 1999) 59/17 (4369-4374).
Refs: 21
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB An **E1B** gene-attenuated adenovirus (dl1520) has been proposed to have a selective cytolytic activity in cancer cells with a mutation or **deletion** in the p53 tumor suppressor gene (p53-null), a defect present in almost half of human hepatocellular carcinomas (HCCs). In this study, the in vitro and in vivo antitumor activity of dl1520 was investigated focusing on two human HCC cell lines, a p53-wild type (p53-wt) cell line and a p53-null cell line. dl1520 was tested for in vitro cytopathic effects and viral replication in the human HCC cell lines Hep3B (p53-null) and HepG2 (p53-wt). The in vivo antitumor effects of dl1520 were investigated in tumors grown s.c. in a severe combined immunodeficient mouse model. In addition, the combination of dl1520 infection with systemic chemotherapy was assessed in these tumor

L13 0 SHUTTLE VECTORS AND L12

=> s vector or vectors and L12

L14 411737 VECTOR OR VECTORS AND L12

=> s 55K gene and p19 gene and PIX gene

L15 0 55K GENE AND P19 GENE AND PIX GENE

=> s 55K gene

L16 16 55K GENE

=> s PIX gene or pIX gene

L17 62 PIX GENE OR PIX GENE

=> s p19 gene

L18 107 P19 GENE

=> s L14 and L15

L19 0 L14 AND L15

=> s L14 and L17

L20 1 L14 AND L17

=> display total ibib abs L20

L20 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:722791 CAPLUS
DOCUMENT NUMBER: 131:347488
TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy
INVENTOR(S): Vogels, Ronald; Bout, Abraham
PATENT ASSIGNEE(S): Introgene B.V., Neth.
SOURCE: Eur. Pat. Appl., 82 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 955373	A2	19991110	EP 1999-201278	19990423
EP 955373	A3	20000419		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9934458	A1	19991116	AU 1999-34458	19990423
PRIORITY APPLN. INFO.:			US 1998-65752	19980424
			WO 1999-N	

L235 19990423
AB The invention discloses novel means and methods for the generation of adenovirus **vectors**. One method of the invention entails a method for generating an adenovirus **vector** comprising welding together two nucleic acid mols. whereby said mols. comprise partially overlapping sequences capable of combining with each other allowing the generation of a phys. linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal, and a nucleic acid of interest or functional parts,

by sequence anal. of all coding exons, exon-intron junctions, and the hepatocyte-specific promotor region including exon Ic)

IT Mutation
(insertion, the PI*Q0saarbruecken allele generated by a 1-bp C-nucleotide insertion within a stretch of seven cytosines is assocd. with undetectable or very low serum levels of .alpha.1-antitrypsin)

IT Genetic element
RL: PRP (Properties)
(intron, genotyping of 15 new .alpha.1-antitrypsin variants was performed by sequence anal. of all coding exons, exon-intron junctions,
and the hepatocyte-specific promotor region including exon Ic)

IT Mutation
(point, the PI*Q0lisbon allele generated by a point mutation resulting in a single amino acid substitution Thr68(ACC).fwdarw.Ile(ATC) is assocd. with undetectable or very low serum levels of .alpha.1-antitrypsin)

IT Genetic element
RL: PRP (Properties)
(promoter, hepatocyte-specific; genotyping of 15 new .alpha.1-antitrypsin variants was performed by sequence anal. of all coding exons, exon-intron junctions, and the hepatocyte-specific promotor region including exon Ic)

IT Mutation
(substitution, the remaining 12 alleles of .alpha.1-antitrypsin gene are assocd. with normal .alpha.1AT serum levels and are characterized by point mutations causing single amino acid substitutions in all but one case)

IT 9041-92-3, .alpha.1-Antitrypsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification and DNA sequence anal. of 15 new .alpha.1-antitrypsin variants, including two PI*Q0 alleles and one deficient PI*M allele)

L10 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2000 ACS
TI Molecular analysis of pulmonary risk gene. Relevance for clinical research, diagnosis, and therapy
AN 1994:554229 CAPLUS
DN 121:154229
TI Molecular analysis of pulmonary risk gene. Relevance for clinical research, diagnosis, and therapy
AU **Poller, Wolfgang Christian**; Faber, Jakob Peter
CS Med. Klin. Poliklin., Klin. Bergmannsheil, Bochum, W-4630/1, Germany
SO Med. Klin. (Munich) (1993), 88(4), 212-30
CODEN: MEKLA7; ISSN: 0723-5003
DT Journal; General Review
LA German
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3
AB A review, with 200 refs. The mol. genetic research on pulmonary diseases as it applies to DNA diagnosis, gene transfer therapy, and pathogenetic anal. is emphasized.
ST review lung disease risk genetics
IT Gene, animal
RL: BIOL (Biological study)
(in lung disease risk, diagnosis and pathogenesis and treatment in relation to, in humans)
IT Lung, disease
(risk for, genes in, diagnosis and pathogenesis and treatment in relation to, in humans)

L10 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2000 ACS
TI Six mutations in the glucokinase gene identified in MODY by using a nonradioactive sensitive screening technique
AN 1994:505791 CAPLUS
DN 121:105791

complexes by low-d. lipoprotein receptor-related protein (LDR)and glycoprotein gp330)

IT 9004-06-2D, Elastase, .alpha.1-antitrypsin complexes 9041-92-3D, .alpha.1-Antitrypsin, elastase complexes 56645-49-9D, Cathepsin G, .alpha.1-antichymotrypsin complexes 141176-92-3D, .alpha.1-Antichymotrypsin, cathepsin G complexes
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(differential recognition of .alpha.1-antitrypsin-elastase and .alpha.1-antichymotrypsin-cathepsin G complexes by low-d. lipoprotein receptor-related protein (LDR)and glycoprotein gp330)

L10 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2000 ACS
TI Identification and DNA sequence analysis of 15 new .alpha.1-antitrypsin variants, including two PI* Q0 alleles and one deficient PI* M allele
AN 1995:309394 CAPLUS
DN 122:232287
TI Identification and DNA sequence analysis of 15 new .alpha.1-antitrypsin variants, including two PI* Q0 alleles and one deficient PI* M allele
AU Faber, Jakob-Peter; **Poller, Wolfgang**; Weidinger, Sebastian; Kirchgesser, Michael; Schwaab, Rainer; Bidlingmaier, Frank; Olek, Klaus
CS Institut Klinische Biochemie, Universitaet Bonn, Bonn, Germany
SO Am. J. Hum. Genet. (1994), 55(6), 1113-121
CODEN: AJHGAG; ISSN: 0002-9297
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 7, 13
AB We have investigated the mol. basis of 15 new .alpha.1-antitrypsin (.alpha.1AT) variants. Phenotyping by isoelec. focusing (IEF) was used as a screening method to detect .alpha.1AT variants at the protein level. Genotyping was then performed by sequence anal. of all coding exons, exon-intron junctions, and the hepatocyte-specific promotor region including exon Ic. Three of these rare variants are alleles of clin. relevance, assocd. with undetectable or very low serum levels of .alpha.1AT: the PI*Q0saarbruecken allele generated by a 1-bp C-nucleotide insertion within a stretch of seven cytosines spanning residues 360-362, resulting in a 3' frameshift and the acquisition of a stop codon at residue 376; a point mutation in the PI*Q0lisbon allele, resulting in a single amino acid substitution Thr68(ACC).fwdarw.Ile(ATC); and an in-frame trinucleotide deletion .DELTA.Phe51 (TTC) in the highly deficient PI*Mpalermo allele. The remaining 12 alleles are assocd. with normal .alpha.1AT serum levels and are characterized by point mutations causing single amino acid substitutions in all but one case. This exception is a silent mutation, which does not affect the amino acid sequence. The limitation of IEF compared with DNA sequence anal., for identification of new variants, their generation by mutagenesis, and the clin. relevance of the three deficiency alleles are discussed.
ST alpha1 antitrypsin variant DNA sequence analysis
IT Deoxyribonucleic acid sequence determination
(identification and DNA sequence anal. of 15 new .alpha.1-antitrypsin variants, including two PI*Q0 alleles and one deficient PI*M allele)
IT Gene, animal
RL: PRP (Properties)
(identification and DNA sequence anal. of 15 new .alpha.1-antitrypsin variants, including two PI*Q0 alleles and one deficient PI*M allele)
IT Mutation
(deletion, an in-frame trinucleotide deletion .DELTA.Phe51 (TTC) in the highly deficient PI*Mpalermo allele is assocd. with undetectable or very low serum levels of .alpha.1-antitrypsin)
IT Genetic element
RL: PRP (Properties)
(exon, genotyping of 15 new .alpha.1-antitrypsin variants was performed

derivs., and/or analogs thereof. A novel packaging cell line, designated 911, is derived from diploid human embryonic retinoblasts (HER) that harbors nucleotides 80-6788 of the adenovirus 5 genome. Novel packaging cell lines are also provided that express just E1A genes and E1B genes without undergoing apoptotic cell death, as occurs in human diploid cells that express E1A in the absence of E1B, and are able to transcomplement E1B-defective recombinant adenoviruses. Packaging constructs that are mutated or deleted for E1B 21-kDa, but just express the 55-kDa protein, and packaging constructs to be used for generation of complementing cell lines from diploid cells without the need of selection with marker genes are also provided. After transfection of HER cells with construct pIG.E1A.E1B, 7 independent cell lines could be established (designated PER.C1 to PER.C9) which express E1A and E1B proteins, are stable, and complement E1-defective adenovirus **vectors**. New adenovirus **vectors** are provided with extended E1 deletions but contain pIX promoter sequences and the **pIX gene**, and are the basis for the development of further deleted adenovirus **vectors** that are mutated for E2A, E2B, or E4.

=> dis his

(FILE 'HOME' ENTERED AT 09:18:30 ON 28 APR 2000)

FILE 'EMBASE' ENTERED AT 09:18:50 ON 28 APR 2000
L1 0 S POLLER W?/AU RAN=(1985)
L2 0 S POLLER/AU RAN=(1985)
L3 0 S POLLER W? AND GERMANY/SO RAN=(1990)

FILE 'EMBASE' ENTERED AT 09:25:50 ON 28 APR 2000
E POLLER W/AU
L4 41 S E3-E5
L5 32 S L4 AND PY>1990
L6 7 S L5 AND ADENOVIRAL

FILE 'CAPLUS' ENTERED AT 09:37:03 ON 28 APR 2000
E POLLER W/AU
L7 25 S E3-E6
L8 0 S L7 AND PY<1999 AND E1
L9 0 S L7 AND E1
L10 25 S L7

FILE 'EMBASE, SCISEARCH, CAPLUS, BIOSIS' ENTERED AT 09:53:00 ON 28 APR 2000

FILE 'MEDLINE, SCISEARCH, CAPLUS, BIOSIS, EMBASE' ENTERED AT 09:53:27 ON 28 APR 2000
L11 3410 S ADENOVIRAL (S) E1B OR E1B OR E1B GENES OR E1B GENES (S) DELET
L12 2982 S L11 AND PY<1999
L13 0 S SHUTTLE VECTORS AND L12
L14 411737 S VECTOR OR VECTORS AND L12
L15 0 S 55K GENE AND P19 GENE AND PIX GENE
L16 16 S 55K GENE
L17 62 S PIX GENE OR PIX GENE
L18 107 S P19 GENE
L19 0 S L14 AND L15
L20 1 S L14 AND L17

=> s L11 and PY<1998 and L14 and L18

2 FILES SEARCHED...
4 FILES SEARCHED...
L21 0 L11 AND PY<1998 AND L14 AND L18

=> s L11 and PY<1998 and L18

2 FILES SEARCHED...
4 FILES SEARCHED...
L22 0 L11 AND PY<1998 AND L18

=> s L11 and L12 and TNF.alpha.

L23 20 L11 AND L12 AND TNF.ALPHA.

=> display total ibib abs

ENTER (L23), L# OR ?:L23

L23 ANSWER 1 OF 20 MEDLINE
ACCESSION NUMBER: 97022998 MEDLINE
DOCUMENT NUMBER: 97022998
TITLE: [Apoptosis and human viral infections].
Apoptose et infections virales humaines.
AUTHOR: Wattre P; Bert V; Hober D
CORPORATE SOURCE: Laboratoire de virologie, batiment IRFPPS, CHRU, Lille, France.
SOURCE: ANNALES DE BIOLOGIE CLINIQUE, **(1996)** 54 (5) 189-97. Ref: 51
Journal code: 4ZS. ISSN: 0003-3898.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY WEEK: 19970104
AB Homeostasis of cell numbers in tissues is maintained by a critical balance
between cell proliferation and programmed cell death or apoptosis. Many human viruses are able to develop suitable strategies for modifying apoptosis in virus-infected cells and in virus-primed T cells. Apoptosis is characterized by the fragmentation of nuclear DNA into 180-200 bp apoptotic bodies and can be analysed microscopically or by flow cytometry using staining with various dyes. Moreover DNA cleavage can be identified by electrophoresis and by specific labeling using in situ nucleotidyltransferase assay (ISNT), terminal deoxynucleotidyltransferase-
mediated dUTP nick-end labeling technique (Tunel), or by Elisa. Adenovirus
E1A induces expression of protooncogenes c-myc and c-fos which sensitize cells to apoptosis; EBV EBNA-5, and adenovirus E1A, HPV E7, and polyomavirus large T act in the same way by displacing pRB-bound E2F. EBV EBNA-5, HPV E6, Adenovirus **E1B** 55 kDa inactivate the tumor suppressor protein p53 and engage the cells in the transformation process.
EBV LMP-1, HHV6, and HTLV1 tax induce the antiapoptotic bcl-2 protein. EBV
BHRF1 encodes proteins with homology to bcl-2 and Adenovirus **E1B** 19 kDa encodes proteins that have protective functions similar to bcl-2. Activated lymphocytes responding to viral infections express high levels of fas and are susceptible to apoptosis. **TNF alpha** can down- or up-regulate fas and down-regulates TNF-R. Adenovirus **E1B** 19 kDa blocks the proapoptotic activity of **TNF alpha**.
Inversly, Cytomegalovirus, hepatitis C virus and Myxoviruses up-regulate fas antigen prior to undergoing apoptosis. In HIV-infected patients, CD4+ T-cell apoptosis is mediated by the cytopathic effect of the virus and the

cell surface expression of gp 120-env protein. Moreover, an accelerated T-cell apoptosis in HIV-infected individuals is characterized by (i) HIV gp120-CD4+ cross-linking and subsequent aberrant signaling of T-cells, (ii) involvement of **TNF alpha**-fas/Apo-1 (TNF-R) binding, (iii) involvement of accessory cells as an apoptosis inducer and as a result of defective antigen presentation, (iv) possible superantigen activity induced by HIV products and cofactors. Many viruses also encode proteins with protease activity which could induce apoptosis. The induction of apoptosis may result in virus clearance, in contrast the inhibition of apoptosis may result in virus cell transformation and viral persistence. Indirectly, the apoptosis of infected cells may be induced by CTLs, NK cells and cytokines. In addition, apoptosis-mediated physiological depletion of T lymphocytes in the course of viral infection can silence the immune response and can induce immunodeficiency.

L23 ANSWER 2 OF 20 MEDLINE
ACCESSION NUMBER: 96145137 MEDLINE
DOCUMENT NUMBER: 96145137
TITLE: Essential role of NF-kappa B in transactivation of the human immunodeficiency virus long terminal repeat by the human cytomegalovirus 1E1 protein.
AUTHOR: Kim S; Yu S S; Kim V N
CORPORATE SOURCE: Institute for Molecular Biology and Genetics, Seoul National University, Kwan-Ak-Gu, Korea.
SOURCE: JOURNAL OF GENERAL VIROLOGY, **(1996 Jan)** 77 (Pt 1) 83-91.
Journal code: I9B. ISSN: 0022-1317.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199605

AB The 72 kDa 1E1 protein of human cytomegalovirus (HCMV) is one of a few viral regulatory proteins expressed immediately after infection of a host cell. Although it is now well-established that 1E1 is a potent transcriptional activator of the human immunodeficiency virus (HIV) long terminal repeat (LTR), the identity of the nucleotide sequence responsive to 1E1 remains elusive and the molecular mechanism of this interaction is not well-understood. We have constructed various LTR mutants and tested them for their ability to be activated by 1E1 using transient transfection assays. Mutations in the NF-kappa B sites, of either a few changes in the nucleotide sequence or a deletion of the entire region, abrogated 1E1-driven transactivation. Deletion of the Tat-responsive element (TAR) had no significant effect on reporter expression. Mutations in the Sp1 sites or the TATA box significantly lowered LTR activity, but this is probably due to an effect on the general transcription system, as these elements are also required for the transactivation of the LTR by many stimulators including Tat, tumour necrosis factor alpha (**TNF-alpha**). E1A/**E1B** and phorbol myristate acetate (PMA). In addition, gel retardation analysis demonstrated that NF- kappa B activity was significantly increased in human T lymphoid H9 and monocytic U937 cell lines constitutively expressing 1E1. Taken together, these data suggest that NF- kappa B plays a central role in the 1E1 transactivation of the HIV LTR.

L23 ANSWER 3 OF 20 MEDLINE
ACCESSION NUMBER: 92269829 MEDLINE
DOCUMENT NUMBER: 92269829
TITLE: The 19-kilodalton adenovirus **E1B** transforming protein inhibits programmed cell death and prevents cytolysis by tumor necrosis factor alpha.
AUTHOR: White E; Sabbatini P; Debbas M; Wold W S; Kusher D I;

Gooding L R
CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine, Piscataway,
New Jersey 08854.
CONTRACT NUMBER: CA13106 (NCI)
CA53370 (NCI)
CA48219 (NCI)
+
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, **(1992 Jun)** 12 (6) 2570-80.
Journal code: NGY. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208

AB The adenovirus E1A and **E1B** proteins are required for transformation of primary rodent cells. When expressed in the absence of the 19,000-dalton (19K) **E1B** protein, however, the E1A proteins are acutely cytotoxic and induce host cell chromosomal DNA fragmentation and cytolysis, analogous to cells undergoing programmed cell death (apoptosis). E1A alone can efficiently initiate the formation of foci which subsequently undergo abortive transformation whereby stimulation of cell growth is counteracted by continual cell death. Cell lines with an immortalized growth potential eventually arise with low frequency. Coexpression of the **E1B** 19K protein with E1A is sufficient to overcome abortive transformation to produce high-frequency transformation.

Like E1A, the tumoricidal cytokine tumor necrosis factor alpha (**TNF-alpha**) evokes a programmed cell death response in many tumor cell lines by inducing DNA fragmentation and cytolysis. Expression of the **E1B** 19K protein by viral infection, by transient expression, or in transformed cells completely and specifically blocks this **TNF-alpha**-induced DNA fragmentation and cell death. Cosegregation of 19K protein transforming activity with protection from **TNF-alpha**-mediated cytolysis demonstrates that both activities are likely the consequence of the same function of the protein. Therefore, we propose that by suppressing an intrinsic cell death mechanism activated by **TNF-alpha** or E1A, the **E1B** 19K protein enhances the transforming activity of E1A and enables adenovirus to evade **TNF-alpha** -dependent immune surveillance.

L23 ANSWER 4 OF 20 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 1999:597317 SCISEARCH
THE GENUINE ARTICLE: 220YD
TITLE: Regulation of apoptosis by adenovirus E1A and **E1B** oncogenes
AUTHOR: White E (Reprint)
CORPORATE SOURCE: RUTGERS STATE UNIV, DEPT MOL BIOL & BIOCHEM, CTR ADV BIOTECHNOL & MED, HOWARD HUGHES MED INST, PISCATAWAY, NJ 08854 (Reprint); RUTGERS STATE UNIV, CANC INST NEW JERSEY,
PISCATAWAY, NJ 08854
COUNTRY OF AUTHOR: USA
SOURCE: SEMINARS IN VIROLOGY, (**AUG 1998**) Vol. 8, No. 6, pp. 505-513.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 1044-5773.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 105
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Adenovirus E1A promotes apoptosis by interacting with and inhibiting negative regulators of cell cycle control. Binding of E1A to, and inhibition of, the transcriptional coadaptor p300 promotes accumulation of the p53 tumor suppressor protein which induces apoptosis. By inhibiting p300, E1A prevents the transcriptional activation of mdm-2, the product of which interacts with and promotes the degradation of p53. Thus the E1A-p300 interaction disables the negative feedback loop to control p53 levels, which left unrestrained, cause apoptosis rather than growth arrest. The **E1B** 19K protein functions analogously to Bcl-2 to inhibit apoptosis by E1A, p53, and multiple other stimuli. The **E1B** 19K protein functions by at least two independent mechanisms to inhibit apoptosis. First, the **E1B** 19K protein binds to the pro-apoptotic Bar protein to prevent loss of mitochondrial membrane potential, caspase activation, and apoptosis. Second, the **E1B** 19K protein inhibits caspase interaction by interfering with the function of adaptor molecules such as FADD and Ced-4 that interact with and activate caspases. By inhibiting FADD-dependent activation of the caspase FLICE, the **E1B** 19K protein can disable both the **TNF-alpha**- and the Fas-mediated death signaling pathways which play an important role in immune surveillance against virus infection and cancer. The **E1B** 19K protein binds to Ced-4, and presumably mammalian Ced-4 homologues, and thereby prevents caspase activation. Thus, the study of the mechanism of regulation of apoptosis by the adenovirus transforming proteins has revealed important regulatory steps in death signaling pathways. (C) 1998 Academic Press.

L23 ANSWER 5 OF 20 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 96:601518 SCISEARCH
THE GENUINE ARTICLE: VB164
TITLE: ROLE OF APOPTOSIS IN THE PATHOGENESIS OF HUMAN VIRUS-DISEASE
AUTHOR: WATTRE P (Reprint); BERT V; HOBER D
CORPORATE SOURCE: CTR HOSP REG & UNIV LILLE, VIROL LAB, BATIMENT IRFPPS, F-59037 LILLE, FRANCE (Reprint),
COUNTRY OF AUTHOR: FRANCE
SOURCE: ANNALES DE BIOLOGIE CLINIQUE, (**1996**) Vol. 54, No. 5, pp. 189-197.
ISSN: 0003-3898.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: French
REFERENCE COUNT: 51

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Homeostasis of cell numbers in tissues is maintained by a critical balance between cell proliferation and programmed cell death or apoptosis.

Many human viruses are able to develop suitable strategies for modifying apoptosis in virus-infected cells and in virus-primed T cells. Apoptosis is characterized by the fragmentation of nuclear DNA into 180-200 bp apoptotic bodies and can be analysed microscopically or by flow cytometry using staining with various dyes. Moreover DNA cleavage can be identified by electrophoresis and by specific labeling using in situ nucleotidytransferase assay (ISNT), terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling technique (Tunel), or by Elisa.

Adenovirus E1A induces expression of pr otooncogenes c-myc and c-fos which sensitize cells to apoptosis; EBV EBNA-5, and adenovirus E1A, HPV E7, and polyomavirus large T act in the same way by displacing pRB-bound E2F. EBV EBNA-5, HPV E6, Adenovirus **E1B** 55 kDa inactivate the tumor suppressor protein p53 and engage the cells in the transformation process.

EBV LMP-1, HHV6, and HTLV1 tax induce the antiapoptotic bcl-2 protein. EBV

BHRF1 encodes proteins with homology to bcl-2 and Adenovirus **E1B** 19 kDa encodes proteins that have protective functions similar to bcl-2. Activated lymphocytes responding to viral infections express high levels of fas and are susceptible to apoptosis. **TNF alpha** can down- or up-regulate fas and down-regulates TNF-R. Adenovirus **E1B** 19 kDa blocks the proapoptotic activity of **TNF alpha**. Inversly, Cytomegalovirus, hepatitis C virus and Myoviruses up-regulate fas antigen prior to undergoing apoptosis. In HIV-infected patients, CD4+ T-cell apoptosis is mediated by the cytopathic effect of the virus and the cell surface expression of gp 120-env protein. Moreover, an accelerated T-cell apoptosis in HIV-infected individuals is characterized by (i) HIV gp120-CD4+ doss-linking and subsequent aberrant signaling of T-cells, (ii) involvement of **TNF alpha**-fas/Apo-1 (TNF-R) binding, (iii) involvement of accessory cells as an apoptosis inducer and as a result of defective antigen presentation, (iv) possible superantigen activity induced by HN products and cofactors. Many viruses also encode proteins with protease activity which could induce apoptosis.

The induction of apoptosis may result in virus clearance, in contrast the inhibition of apoptosis mag result in virus cell transformation and viral persistence. Indirectly, the apoptosis of infected cells may be induced by CTLs, NK cells and cytokines. In addition, apoptosis-mediated physiological depletion of T lymphocytes in the course of viral infection can silence the immune response and can induce immunodeficiency.

L23 ANSWER 6 OF 20 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 96:67140 SCISEARCH
THE GENUINE ARTICLE: TP215
TITLE: ESSENTIAL ROLE OF NF-KAPPA-B IN TRANSACTIVATION OF THE HUMAN-IMMUNODEFICIENCY-VIRUS LONG TERMINAL REPEAT BY THE HUMAN CYTOMEGALOVIRUS IE1 PROTEIN
AUTHOR: KIM S Y (Reprint); YU S S; KIM V N
CORPORATE SOURCE: SEOUL NATL UNIV, INST MOLEC BIOL & GENET, KWAN AK GU, BLDG 105, SEOUL 151742, SOUTH KOREA (Reprint)
COUNTRY OF AUTHOR: SOUTH KOREA
SOURCE: JOURNAL OF GENERAL VIROLOGY, (**JAN 1996**) Vol. 77, Part 1, pp. 83-91.
ISSN: 0022-1317.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The 72 kDa IE1 protein of human cytomegalovirus (HCMV) is one of a few viral regulatory proteins expressed immediately after infection of a host cell. Although it is now well-established that IE1 is a potent transcriptional activator of the human immunodeficiency virus (HIV) long terminal repeat (LTR), the identity of the nucleotide sequence responsive to IE1 remains elusive and the molecular mechanism of this interaction is not well-understood. We have constructed various LTR mutants and tested them for their ability to be activated by IE1 using transient transfection assays. Mutations in the NF-kappa B sites, of either a few changes in the nucleotide sequence or a deletion of the entire region, abrogated IE1-driven transactivation. Deletion of the Tat-responsive element (TAR) had no significant effect on reporter expression. Mutations in the Sp1 sites or the TATA box significantly lowered LTR activity, but this is probably due to an effect on the general transcription system, as these elements are also required for the transactivation of the LTR by many stimulators including Tat, tumour necrosis factor alpha (**TNF-alpha**), E1A/**E1B** and phorbol myristate acetate (PMA). In addition, gel retardation analysis demonstrated that NF-kappa B activity was significantly increased in human T lymphoid H9 and monocytic U937 cell

lines constitutively expressing IE1. Taken together, these data suggest that NF-kappa B plays a central role in the IE1 transactivation of the HIV LTR.

L23 ANSWER 7 OF 20 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 94:486537 SCISEARCH
THE GENUINE ARTICLE: NZ494
TITLE: THE MOLECULAR-BASIS OF ADENOVIRUS PATHOGENESIS
AUTHOR: GINSBERG H S (Reprint); PRINCE G A
CORPORATE SOURCE: NIAID, INFECT DIS LAB, TWIN BROOK 2, 12441 PARK LAWN DR, ROCKVILLE, MD, 20852 (Reprint); COLUMBIA UNIV COLL PHYS & SURG, DEPT MICROBIOL, NEW YORK, NY, 10032; COLUMBIA UNIV COLL PHYS & SURG, DEPT MED, NEW YORK, NY, 10032
COUNTRY OF AUTHOR: USA
SOURCE: INFECTIOUS AGENTS AND DISEASE-REVIEWS ISSUES AND COMMENTARY, (**FEB 1994**) Vol. 3, No. 1, pp. 1-8. ISSN: 1056-2044.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The pathology of type 5 (Ad5) pneumonia in Sigmodon hispidus cotton rats is closely similar to that in humans. Virus replicates in bronchiolar epithelial cells, but in situ hybridization shows early gene expression in macrophage/monocytes in alveoli and hilar lymph nodes. Only early gene expression is required to produce the pathology of which there is an ''early'' and a ''late'' phase. The early region 3 (E3), which does not function in viral replication, plays an important role in the natural history of at least the subgroup C adenoviruses (types 1, 2, 5, 6), which produce latent infections in host-infected lymphocytes: The 19-kDa glycoprotein markedly reduces the transport of the class I MHC to the surface of infected cells and, therefore, the attack of cytotoxic T cells, which could eliminate infected cells. When this gene is mutated, the late-phase inflammatory response to infection is markedly increased. The E3 14.7-kDa protein reduces the presence of polymorphonuclear leukocytes in the early-phase pathological inflammatory exudate. The **E1B** 55-kDa is essential to effect the late phase, and when its gene is mutated, the inflammation is greatly reduced although viral replication is not affected. Because only early genes are required to induce the complete pathogenesis of adenovirus infection in cotton rats, it is possible to produce the same pneumonia in lungs of mice in which only adenovirus early genes are expressed. In the unique mouse model, it was possible to demonstrate that tumor necrosis factor (**TNF**)-**alpha**, interleukin-1, (IL-1), and IL-6 cytokines are elaborated during the first 2 to 3 days after infection, but only **TNF-alpha** plays a major role in the early phase of pathogenesis. In nude mice, the late inflammatory response does not appear, indicating that it primarily consists of T cells. Steroids almost completely eliminate the pneumonic inflammatory response to infection.

L23 ANSWER 8 OF 20 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 92:336148 SCISEARCH
THE GENUINE ARTICLE: HV309
TITLE: THE 19-KILODALTON ADENOVIRUS **E1B** TRANSFORMING PROTEIN INHIBITS PROGRAMMED CELL-DEATH AND PREVENTS CYTOLYSIS BY TUMOR-NECROSIS-FACTOR-ALPHA
AUTHOR: WHITE E (Reprint); SABBATINI P; DEBBAS M; WOLD W S M;

KUSHER D I; GOODING L R
CORPORATE SOURCE: CTR ADV BIOTECHNOL & MED, 679 HOES LANE, PISCATAWAY, NJ, 08854 (Reprint); COLD SPRING HARBOR LAB, COLD SPRING HARBOR, NY, 11724; ST LOUIS UNIV, SCH MED, INST MOLEC VIROL, ST LOUIS, MO, 63110; EMORY UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, ATLANTA, GA, 30322
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (**JUN 1992**) Vol. 12, No. 6, pp. 2570-2580.
ISSN: 0270-7306.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 76
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The adenovirus E1A and **E1B** proteins are required for transformation of primary rodent cells. When expressed in the absence of the 19,000-dalton (19K) **E1B** protein, however, the E1A proteins are acutely cytotoxic and induce host cell chromosomal DNA fragmentation and cytolysis, analogous to cells undergoing programmed cell death (apoptosis). E1A alone can efficiently initiate the formation of foci which subsequently undergo abortive transformation whereby stimulation of cell growth is counteracted by continual cell death. Cell lines with an immortalized growth potential eventually arise with low frequency. Coexpression of the **E1B** 19K protein with E1A is sufficient to overcome abortive transformation to produce high-frequency transformation.

Like E1A, the tumoricidal cytokine tumor necrosis factor alpha (**TNF-alpha**) evokes a programmed cell death response in many tumor cell lines by inducing DNA fragmentation and cytolysis. Expression of the **E1B** 19K protein by viral infection, by transient expression, or in transformed cells completely and specifically blocks this **TNF-alpha**-induced DNA fragmentation and cell death. Cosegregation of 19K protein transforming activity with protection from **TNF-alpha**-mediated cytolysis demonstrates that both activities are likely the consequence of the same function of the protein. Therefore, we propose that by suppressing an intrinsic cell death mechanism activated by **TNF-alpha** or E1A, the **E1B** 19K protein enhances the transforming activity of E1A and enables adenovirus to evade **TNF-alpha** -dependent immune surveillance.

L23 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:584507 CAPLUS
DOCUMENT NUMBER: 130:2522
TITLE: Regulation of apoptosis by adenovirus E1A and **E1B** oncogenes
AUTHOR(S): White, Eileen
CORPORATE SOURCE: Howard Hughes Medical Institute, Center for Advanced Biotechnology and Medicine, Department of Molecular Biology and Biochemistry, Rutgers University, Piscataway, NJ, 08854, USA
SOURCE: Semin. Virol. (**1998**), 8(6), 505-513
CODEN: SEVIEL; ISSN: 1044-5773
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 106 refs. Adenovirus E1A promotes apoptosis by interacting with and inhibiting neg. regulators of cell cycle control. Binding of E1A to, and inhibition of, the transcriptional coadaptor p300 promotes accumulation of the p53 tumor suppressor protein which induces apoptosis. By inhibiting p300, E1A prevents the transcriptional activation of mdm-2, the product of which interacts with and promotes the degrdn. of p53. Thus

gp120-CD4+ crosslinking and subsequent aberrant signaling of T-cells (ii) involvement of **TNF alpha**-fas/Apo-1 (TNF-R) binding, (iii) involvement of accessory cells as an apoptosis inducer and as a result of defective antigen presentation, (i.v.) possible superantigen activity induced by HIV products and cofactors. Many viruses also encode proteins with protease activity which could induce apoptosis. The induction of apoptosis may result in virus clearance, in contrast the inhibition of apoptosis may results in virus cell transformation and viral persistence. Indirectly, the apoptosis of infected cells may be induced by CTLs, NK cells and cytokines. In addn., apoptosis-mediated physiol. depletion of T lymphocytes in the course of viral infection can silence the immune response and can induce immunodeficiency.

L23 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:33927 CAPLUS
DOCUMENT NUMBER: 124:108787
TITLE: Essential role of NF-.kappa.B in transactivation of the human immunodeficiency virus long terminal repeat by the human cytomegalovirus IE1 protein
AUTHOR(S): Kim, Sunyoung; Yu, Seung Shin; Kim, Vic Narry
CORPORATE SOURCE: Inst. Mol. Biol. Genetics, Seoul Natl. Univ., Seoul, 151-742, S. Korea
SOURCE: J. Gen. Virol. (**1996**), 77(1), 83-91
CODEN: JGVIAY; ISSN: 0022-1317
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 72 kDa IE1 protein of human cytomegalovirus (HCMV) is one of a few viral regulatory proteins expressed immediately after infection of a host cell. Although it is now well-established that IE1 is a potent transcriptional activator of the human immunodeficiency virus (HIV) long terminal repeat (LTR), the identity of the nucleotide sequence responsive to IE1 remains elusive and the mol. mechanism of this interaction is not well-understood. We have constructed various LTR mutants and tested them for their ability to be activated by IE1 using transient transfection assays. Mutations in the NF-.kappa.B sites, of either a few changes in the nucleotide sequence or a deletion of the entire region, abrogated IE1-driven transactivation. Deletion of the Tat-responsive element (TAR) had no significant effect on reporter expression. Mutations in the Sp1 sites or the TATA box significantly lowered LTR activity, but this is probably due to an effect on the general transcription system, as these elements are also required for the transactivation of the LTR by many stimulators including Tat, tumor necrosis factor alpha (**TNF-.alpha.**), E1A/**E1B** and phorbol myristate acetate (PMA). In addn., gel retardation anal. demonstrated that NF-.kappa.B activity was significantly increased in human T lymphoid H9 and monocytic U937 cell lines constitutively expressing IE1. Taken together, these data suggest that NF-.kappa.B plays a central role in the IE1 transactivation of the HIV LTR.

L23 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:430050 CAPLUS
DOCUMENT NUMBER: 122:236357
TITLE: A new look at an old virus: Molecular pathogenesis of Adenovirus pneumonia
AUTHOR(S): Ginsberg, Harold S.
CORPORATE SOURCE: College Physicians and Surgeons, Columbia University, New York, NY, 10032, USA
SOURCE: Virus Strategies (**1993**), 473-9. Editor(s): Doerfler, Walter; Boehm, Petra. VCH: Weinheim, Germany.
CODEN: 60ZKAT
DOCUMENT TYPE: Conference; General Review

the E1A-p300 interaction disables the neg. feedback loop to control p53 levels, which left unrestrained, cause apoptosis rather than growth arrest. The **E1B** 19K protein functions analogously to Bcl-2 to inhibit apoptosis by E1A, p53, and multiple other stimuli. The **E1B** 19K protein functions by at least two independent mechanisms to inhibit apoptosis. First, the **E1B** 19K protein binds to the pro-apoptotic Bax protein to prevent loss of mitochondrial membrane potential, caspase activation, and apoptosis. Second, the **E1B** 19K protein inhibits caspase interaction by interfering with the function of adaptor mols. such as FADD and Ced-4 that interact with and activate caspases. By inhibiting FADD-dependent activation of the caspase FLICE, the **E1B** 19K protein can disable both the **TNF-.alpha.**- and the Fas-mediated death signaling pathways which play an important role in immune surveillance against virus infection and cancer. The **E1B** 19K protein binds to Ced-4, and presumably mammalian Ced-4 homologs, and thereby prevents caspase activation. Thus, the study of the mechanism of regulation of apoptosis by the adenovirus transforming proteins has revealed important regulatory steps in death signaling pathways. (c) 1998 Academic Press.

L23 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:522933 CAPLUS
DOCUMENT NUMBER: 125:192067
TITLE: Apoptosis and the pathogenesis of human viral disease
AUTHOR(S): Wattre, P.; Bert, V.; Hober, D.
CORPORATE SOURCE: Laboratoire de virologie, CHRU, Lille, 59037, Fr.
SOURCE: Ann. Biol. Clin. (**1996**), 54(5), 189-197
CODEN: ABCLAI; ISSN: 0003-3898
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French

AB A review with 51 refs. Homeostasis of cell nos. in tissues is maintained by a crit. balance between cell proliferation and programmed cell death or apoptosis. Many human viruses are able to develop suitable strategies for modifying apoptosis in virus-infected cells and in virus-primed T cells. Apoptosis is characterized by the fragmentation of nuclear DNA into 180-200 bp apoptotic bodies and can be analyzed microscopically or by flow cytometry using staining with various dyes. Moreover DNA cleavage can be identified by electrophoresis and by specific labeling using in situ nucleotidyltransferase assay (ISNT), terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling technique (Tunel), or by Elisa. Adenovirus E1A induces expression of protooncogenes c-myc and c-fos which sensitize cells to apoptosis; EBV EBNA-5, and adenovirus E1A, HPV E7, and polyomavirus large T act in the same way by displacing pRB-bound E2F. EBV ENBA-5, HPV E6, Adenovirus **E1B** 55 kDa inactivate the tumor suppressor protein p53 and engage the cells in the transformation process. EBV LMP-1, HHV6M and HTLV1 tax induce the antiapoptotic bcl-2 protein. EBV BHRF1 encodes proteins with homol. to bcl-2 and Adenovirus **E1B** 19 kDa encodes proteins that have protective functions similar to bcl-2. Activated lymphocytes responding to viral infections express high levels of fas are susceptible to apoptosis. **TNF.alpha.** can down- or up-regulate fas and down-regulates TNF-R. Adenovirus **E1B** 19 kDa blocks the proapoptotic activity of **TNF.alpha.**. Inversely, Cytomegalovirus, hepatitis C virus and Myxoviruses up-regulate fas antigen prior to undergoing apoptosis. In HIV-infected patients, CD4+ T-cell apoptosis is mediated by the cytopathic effect of the virus and the cell surface expression of gp120-env protein. Moreover, an accelerated T-cell apoptosis in HIV-infected individuals is characterized by (i) HIV

LANGUAGE: English

AB A review with 23 refs. on the mol. pathogenesis of adenovirus infections. The results indicate that only the expression of early genes is required for infection. Early genes E1A, **E1B**, and E3 are important. These genes, and possibly others, induce an early, inflammatory phase which the cytokine **TNF-.alpha.**, and possibly others, produce. A cytotoxic T-cell response induces the late phase.

L23 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1992:446333 CAPLUS

DOCUMENT NUMBER: 117:46333

TITLE: The 19-kilodalton adenovirus **E1B** transforming protein inhibits programmed cell death and prevents cytolysis by tumor necrosis factor .alpha.

AUTHOR(S): White, Eileen; Sabbatini, Peter; Debbas, Michael; Wold, William S. M.; Kusher, David I.; Gooding, Linda R.

CORPORATE SOURCE: Cent. Adv. Biotechnol. Med., Piscataway, NJ, 08854, USA

SOURCE: Mol. Cell. Biol. (**1992**), 12(6), 2570-80
CODEN: MCEBD4; ISSN: 0270-7306

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The adenovirus E1A and **E1B** proteins are required for transformation of primary rodent cells. When expressed in the absence of the 19,000-dalton (19K) **E1B** protein, however, the E1A proteins are acutely cytotoxic and induce host cell chromosomal DNA fragmentation and cytolysis, analogous to cells undergoing programmed cell death (apoptosis). E1A alone can efficiently initiate the formation of foci which subsequently undergo abortive transformation whereby stimulation of cell growth is counteracted by continual cell death. Cell lines with an immortalized growth potential eventually arise with low frequency. Coexpression of the **E1B** 19K protein with E1A is sufficient to overcome abortive transformation to produce high-frequency transformation.

Like E1A, the tumoricidal cytokine tumor necrosis factor .alpha. (**TNF-.alpha.**) evokes a programmed cell death response in many tumor cell lines by inducing DNA fragmentation and cytolysis. Expression of the **E1B** 19K protein by viral infection, by transient expression, or in transformed cells completely and specifically blocks this **TNF-.alpha.**-induced DNA fragmentation and cell death. Cosegregation of 19K protein transforming activity with protection from **TNF-.alpha.**-mediated cytolysis demonstrates that both activities are likely the consequence of the same function of the protein. Therefore, the authors propose that by suppressing an intrinsic cell death mechanism activated by **TNF-.alpha.** or E1A, the **E1B** 19K protein enhances the transforming activity of E1A and enables adenovirus to evade **TNF-.alpha.**-dependent immune surveillance.

L23 ANSWER 14 OF 20 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1996:464353 BIOSIS

DOCUMENT NUMBER: PREV199699186709

TITLE: Role of apoptosis in the pathogenesis of human virus disease.

AUTHOR(S): Wattre, P. (1); Bert, V.; Hober, D.

CORPORATE SOURCE: (1) Lab. de virol., batiment IRFPPS, CHRU, 59037 Lille Cedex France

SOURCE: Annales de Biologie Clinique, (1996) Vol. 54, No. 5, pp. 189-197.
ISSN: 0003-3898.

DOCUMENT TYPE: General Review

LANGUAGE: French

SUMMARY LANGUAGE: French; English

'AB Homeostasis of cell numbers in tissues is maintained by a critical balance
between cell proliferation and programmed cell death or apoptosis. Many human viruses are able to develop suitable strategies for modifying apoptosis in virus-infected cells and in virus-primed T cells. Apoptosis is characterized by the fragmentation of nuclear DNA into 180-200 bp apoptotic bodies and can be analysed microscopically or by flow cytometry using staining with various dyes. Moreover DNA cleavage can be identified by electrophoresis and by specific labeling using in situ nucleotidytransferase assay (ISNT), terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling technique (Tunel), or by Elisa.
Adenovirus
E1A induces expression of protooncogenes c-myc and c-fos which sensitize cells to apoptosis; EBV EBNA-5, and adenovirus E1A, HPV E7, and polyomavirus large T act in the same way by displacing pRB-bound E2F. EBV EBNA-5, HPV E6, Adenovirus **E1B** 55 kDa inactivate the tumor suppressor protein p53 and engage the cells in the transformation process.
EBV LMP-1, HHV6, and HTLV1 tax induce the antiapoptotic bcl-2 protein.
EBV
BHRF1 encodes proteins with homology to bcl-2 and Adenovirus **E1B** 19 kDa encodes proteins that have protective functions similar to bcl-2. Activated lymphocytes responding to viral infections express high levels of fas and are susceptible to apoptosis. **TNF-alpha** can down- or up-regulate fas and down-regulates TNF-R. Adenovirus **E1B** 19 kDa blocks the proapoptotic activity of **TNF-alpha**.
Inversely, Cytomegalovirus, hepatitis C virus and Myxoviruses up-regulate fas antigen prior to undergoing apoptosis. In HIV-infected patients, CD4+ T-cell apoptosis is mediated by the cytopathic effect of the virus and the
cell surface expression of gp 120-env protein. Moreover, on accelerated T-cell apoptosis in HIV-infected individuals is characterized by (i) HIV gp120-CD4+ cross-linking and subsequent aberrant signaling of T-cells, (ii) involvement of **TNF alpha**-fas/Apo-1 (TNF-R) binding, (iii) involvement of accessory cells as an apoptosis inducer and as a result of defective antigen presentation, (iv) possible superantigen activity induced by HIV products and cofactors. Many viruses also encode proteins with protease activity which could induce apoptosis. The induction of apoptosis may result in virus cell clearance, in contrast the
inhibition of apoptosis may result in virus cell transformation and viral persistence. Indirectly, the apoptosis of infected cells may be induced by
CTs, NK cells and cytokines. In addition, apoptosis-mediated physiological
depletion of T lymphocytes in the course of viral infection can silence the immune response and can induce immunodeficiency.

L23 ANSWER 15 OF 20 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:75974 BIOSIS
DOCUMENT NUMBER: PREV199698648109
TITLE: Essential role of NF-kappa-B in transactivation of the human immunodeficiency virus long terminal repeat by the human cytomegalovirus IE1 protein.
AUTHOR(S): Kim, Sunyoung (1); Yu, Seung Shin; Kim, Vic Narry
CORPORATE SOURCE: (1) Inst. Mol. Biol. Genetics, Build. 105 Seoul Natl. Univ., Kwan-Ad-Gu, Seoul 151-742 South Korea
SOURCE: Journal of General Virology, (1996) Vol. 77, No. 1, pp. 83-91.
ISSN: 0022-1317.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The 72 kDa IE1 protein of human cytomegalovirus (HCMV) is one of a few viral regulatory proteins expressed immediately after infection of a host cell. Although it is now well-established that IE1 is a potent

transcriptional activator of the human immunodeficiency virus (HIV) long terminal repeat (LTR), the identity of the nucleotide sequence responsive to IE1 remains elusive and the molecular mechanism of this interaction is not well-understood. We have constructed various LTR mutants and tested them for their ability to be activated by IE1 using transient transfection assays. Mutations in the NF-kappa-B sites, of either a few changes in the nucleotide sequence or a deletion of the entire region, abrogated IE1-driven transactivation. Deletion of the Tat-responsive element (TAR) had no significant effect on reporter expression. Mutations in the Sp1 sites or the TATA box significantly lowered LTR activity, but this is probably due to an effect on the general transcription system, as these elements are also required for the transactivation of the LTR by many stimulators including Tat, tumour necrosis factor alpha (**TNF-alpha**), E1A/**E1B** and phorbol myristate acetate (PMA). In addition, gel retardation analysis demonstrated that NF-kappa-B activity was significantly increased in human T lymphoid H9 and monocytic U937 cell lines constitutively expressing IE1. Taken together, these data suggest that NF-kappa-B plays a central role in the IE1 transactivation of the HIV LTR.

L23 ANSWER 16 OF 20 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1992:349418 BIOSIS
DOCUMENT NUMBER: BA94:41643
TITLE: THE 19-KILODALTON ADENOVIRUS **E1B** TRANSFORMING PROTEIN INHIBITS PROGRAMMED CELL DEATH AND PREVENTS CYTOLYSIS BY TUMOR NECROSIS FACTOR ALPHA.
AUTHOR(S): WHITE E; SABBATINI P; DEBBAS M; WOLD W S M; KUSHER D I; GOODING L R
CORPORATE SOURCE: COLD SPRING HARBOR LAB., COLD SPRING HARBOR, NEW YORK 11724.
SOURCE: MOL CELL BIOL, (1992) 12 (6), 2570-2580.
CODEN: MCEBD4. ISSN: 0270-7306.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The adenovirus E1A and **E1B** proteins are required for transformation of primary rodent cells. When expressed in the absence of the 19,000-dalton (19K) **E1B** protein, however, the E1A proteins are acutely cytotoxic and induce host cell chromosomal DNA fragmentation and cytolysis, analogous to cells undergoing programmed cell death (apoptosis). E1A alone can efficiently initiate the formation of foci which subsequently undergo abortive transformation whereby stimulation of cell growth is counteracted by continual cell death. Cell ines with an immortalized growth potential eventually arise with low frequency. Coexpression of the **E1B** 19K protein with E1A is sufficient to overcome abortive transformation to produce high-frequency transformation.
Like E1A, the tumoricidal cytokine tumor necrosis factor .alpha. (**TNF-.alpha.**) evokes a programmed cell death response in many tumor cell lines by inducing DNA fragmentation and cytolysis. Expression of the **E1B** 19K protein by viral infection, by transient expression, or in transformed cells completely and specifically blocks this **TNF-.alpha.**-induced DNA fragmentation and cell death. Cosegregation of 19K protein transforming actvity with protection from **TNF-.alpha.**-mediated cytolysis demonstrates that both activities are likely the consequence of the same function of the protein. Therefore, we propose that by suppressing an intrinsic cell death mechanism activated by **TNF-.alpha**. or E1A, the **E1B** 19K protein enhances the transforming activity of E1A and enables adenovirus to evade **TNF-.alpha**.-dependent immune surveillance.

L23 ANSWER 17 OF 20 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998321445 EMBASE
TITLE: Regulation of apoptosis by adenovirus E1A and **E1B** oncogenes.
AUTHOR: White E.
CORPORATE SOURCE: E. White, Howard Hughes Medical Institute, Ctr. Advanced Biotechnology Medicine, Dept. Molecular Biology Biochemistry, Piscataway, NJ 08854, United States
SOURCE: Seminars in Virology, (1998) 8/6 (505-513).
Refs: 106
ISSN: 1044-5773 CODEN: SEVIEL
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adenovirus E1A promotes apoptosis by interacting with and inhibiting negative regulators of cell cycle control. Binding of E1A to, and inhibition of, the transcriptional coadaptor p300 promotes accumulation of the p53 tumor suppressor protein which induces apoptosis. By inhibiting p300, E1A prevents the transcriptional activation of mdm-2, the product of which interacts with and promotes the degradation of p53. Thus the E1A-p300 interaction disables the negative feedback loop to control p53 levels, which left unrestrained, cause apoptosis rather than growth arrest. The **E1B** 19K protein functions analogously to Bcl-2 to inhibit apoptosis by E1A, p53, and multiple other stimuli. The **E1B** 19K protein functions by at least two independent mechanisms to inhibit apoptosis. First, the **E1B** 19K protein binds to the pro-apoptotic Bax protein to prevent loss of mitochondrial membrane potential, caspase activation, and apoptosis. Second, the **E1B** 19K protein inhibits caspase interaction by interfering with the function of adaptor molecules such as FADD and Ced-4 that interact with and activate caspases. By inhibiting FADD-dependent activation of the caspase FLICE, the **E1B** 19K protein can disable both the **TNF-.alpha.**- and the Fas-mediated death signaling pathways which play an important role in immune surveillance against virus infection and cancer. The **E1B** 19K protein binds to Ced-4, and presumably mammalian Ced-4 homologues, and thereby prevents caspase activation. Thus, the study of the mechanism of regulation of apoptosis by the adenovirus transforming proteins has revealed important regulatory steps in death signaling pathways.

L23 ANSWER 18 OF 20 EMBASE
ACCESSION NUMBER: 96036615 EMBASE
DOCUMENT NUMBER: 1996036615
TITLE: Essential role of IVF-.kappa.B in transactivation of the human immunodeficiency virus long terminal repeat by the human cytomegalovirus IE1 protein.
AUTHOR: Kim S.; Yu S.S.; Kim V.N.
CORPORATE SOURCE: Institute Molecular Biology Genetics, Bldg. 105 Seoul National University,Kwan-Ak-Gu, Seoul 151-742, Korea, Republic of
SOURCE: Journal of General Virology, (1996) 77/1 (83-91).
ISSN: 0022-1317 CODEN: JGVIAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The 72 kDa IE1 protein of human cytomegalovirus (HCMV) is one of a few viral regulatory proteins expressed immediately after infection of a host cell. Although it is now well-established that IE1 is a potent transcriptional activator of the human immunodeficiency virus (HIV) long

terminal repeat (LTR), the identity of the nucleotide sequence responsive to IE1 remains elusive and the molecular mechanism of this interaction is not well-understood. We have constructed various LTR mutants and tested them for their ability to be activated by IE1 using transient transfection assays. Mutations in the NF-.kappa.B sites, of either a few changes in the nucleotide sequence or a deletion of the entire region, abrogated IE1-driven transactivation. Deletion of the Tat-responsive element (TAR) had no significant effect on reporter expression. Mutations in the Sp1 sites or the TATA box significantly lowered LTR activity, but this is probably due to an effect on the general transcription system, as these elements are also required for the transactivation of the LTR by many stimulators including Tat, tumour necrosis factor alpha (**TNF-.alpha.**), E1A/**E1B** and phorbol myristate acetate (PMA). In addition, gel retardation analysis demonstrated that NF-.kappa.B activity was significantly increased in human T lymphoid H9 and monocytic U937 cell lines constitutively expressing IE1. Taken together, these data suggest that NF-.kappa.B plays a central role in the IE1 transactivation of the HIV LTR.

L23 ANSWER 19 OF 20 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94235426 EMBASE
DOCUMENT NUMBER: 1994235426
TITLE: The molecular basis of adenovirus pathogenesis.
AUTHOR: Ginsberg H.S.; Prince G.A.
CORPORATE SOURCE: NIH, Twin Brook II, 12441 Park Lawn Drive,Rockville, MD 20852, United States
SOURCE: Infectious Agents and Disease, (1994) 3/1 (1-8).
ISSN: 1056-2044 CODEN: IADIEV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The pathology of type 5 (Ad5) pneumonia in Sigmodon hispidus cotton rats is closely similar to that in humans. Virus replicates in bronchiolar epithelial cells, but in situ hybridization shows early gene expression in macrophage/monocytes in alveoli and hilar lymph nodes. Only early gene expression is required to produce the pathology of which there is an 'early' and a 'late' phase. The early region 3 (E3), which does not function in viral replication, plays an important role in the natural history of at least the subgroup C adenoviruses (types 1, 2, 5, 6), which produce latent infections in host-infected lymphocytes: The 19-kDa glycoprotein markedly reduces the transport of the class I MHC to the surface of infected cells and, therefore, the attack of cytotoxic T cells, which could eliminate infected cells. When this gene is mutated, the late-phase inflammatory response to infection is markedly increased. The E3 14.7-kDa protein reduces the presence of polymorphonuclear leukocytes in the early-phase pathological inflammatory exudate. The **E1B** 55-kDa is essential to effect the late phase, and when its gene is mutated, the inflammation is greatly reduced although viral replication is not affected. Because only early genes are required to induce the complete pathogenesis of adenovirus infection in cotton rats, it is possible to produce the same pneumonia in lungs of mice in which only adenovirus early genes are expressed. In the unique mouse model, it was possible to demonstrate that tumor necrosis factor (**TNF**)-.**alpha**., interleukin-I, (IL-1), and IL-6 cytokines are elaborated during the first 2 to 3 days after infection, but only **TNF**-.**alpha**.

plays a major role in the early phase of pathogenesis. In nude mice, the late inflammatory response does not appear, indicating that it primarily consists of T cells. Steroids almost completely eliminate the pneumonic inflammatory response to infection.

L23 ANSWER 20 OF 20 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92210480 EMBASE
DOCUMENT NUMBER: 1992210480
TITLE: The 19-kilodalton adenovirus **E1B** transforming protein inhibits programmed cell death and prevents cytolysis by tumor necrosis factor .alpha..
AUTHOR: White E.; Sabbatini P.; Debbas M.; Wold W.S.M.; Kusher D.I.; Gooding L.R.
CORPORATE SOURCE: Advanced Biotechnology/Medicine Ctr., 679 Hoes Lane,Piscataway, NJ 08854, United States
SOURCE: Molecular and Cellular Biology, (1992) 12/6 (2570-2580). ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The adenovirus E1A and **E1B** proteins are required for transformation of primary rodent cells. When expressed in the absence of the 19,000-dalton (19K) **E1B** protein, however, the E1A proteins are acutely cytotoxic and induce host cell chromosomal DNA fragmentation and cytolysis, analogous to cells undergoing programmed cell death (apoptosis). E1A alone can efficiently initiate the formation of foci which subsequently undergo abortive transformation whereby stimulation of cell growth is counteracted by continual cell death. Cell lines with an immortalized growth potential eventually arise with low frequency. Coexpression of the **E1B** 19K protein with E1A is sufficient to overcome abortive transformation to produce high- frequency transformation. Like E1A, the tumoricidal cytokine tumor necrosis factor .alpha. (**TNF**-.**alpha**.) evokes a programmed cell death response in many tumor cell lines by inducing DNA fragmentation and cytolysis. Expression of the **E1B** 19K protein by viral infection, by transient expression, or in transformed cells completely and specifically blocks this **TNF**-.**alpha**.-induced DNA fragmentation and cell death. Cosegregation of 19K protein transforming activity with protection from **TNF**-.**alpha**.-mediated cytolysis demonstrates that both activities are likely the consequence of the same function of the protein. Therefore, we propose that by suppressing an intrinsic cell death mechanism activated by **TNF**-.**alpha**. or E1A, the **E1B** 19K protein enhances the transforming activity of E1A and enables adenovirus to evade **TNF**-.**alpha**.-dependent immune surveillance.

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